REMARKS

The new claim is drawn to a preferred aspect of the invention. This claim should not be restricted from the other claims of this application because it plainly relates to the use of the galenical formulations which is described in the specification. Should the claim be restricted, applicants will request reinstatement of such method claim, along with claims 32-38, since these will be based on the particulars of the galenical formulation claims.

The prior art rejection is untenable because there is no motivation to combine the two cited references. Whereas, Platzek et al. does relate to the field of this invention, i.e., the use of certain perflouroalkyl-containing compounds as contrast agents in magnetic resonance imaging, especially H-based, T_1-weighted imaging, Milius has nothing to do with such imaging. Rather, Milius relates to a certain new perflouroalkyl-containing compound which is particularly effective as an emulsifier of various fluorocarbon compositions. See, for example, the Abstract, the second paragraph (describing the article as involving surfactants), the third paragraph of the article describing it as involving emulsification abilities, etc. There is no reason for a skilled worker to combine Milius with Platzek et al. to provide a new galenical formulation useful as a contrast medium, or for any other purpose.

As the examiner notes, Milius describes various other fluorocarbons as being useful for a variety of purposes, including as contrast agents. In this regard, Milius refers to, among others, Mattrey, being submitted herewith. This article does deal with a perflouroalkyl-containing contrast agent which is used for MR imaging. However, it makes clear that there is no motivation to combine such agents (diamagnetic agents as recited in the claims) with the paramagnetic agents of Platzek et al.

Of course, the Platzek et al. paramagnetic agents are used as contrast media because their paramagnetism has an influence on an MR image. These are most often used as T_1-

imaging contrast agents because their paramagnetism influences the T_1 relaxation time. On the other hand, Mattrey points out in the paragraph bridging pages 249-251, that its diamagnetic compounds produce a "signal void," i.e., they "darken" both T_1- and T_2-weighted images. This is because they generate no magnetic effects themselves. They are diamagnetic! Instead, on such images, they act like barium does in an x-ray image, i.e., they themselves appear as dark material and are themselves thus "imaged". However, Platzek's paramagnetic contrast agents are administered not to be imaged themselves, but rather to influence and enhance the images of other components, i.e., typically, water in the body. Since diamagnetic fluorocarbon agents operate in a completely different way, there is no motivation to combine such agents with paramagnetic agents.

Mattrey also discloses that its diamagnetic fluorocarbons can be used in a different kind of imaging, i.e., ^{19}F imaging to themselves be imaged because of the presence of the fluorine atom on the molecules. Such imaging is conducted on a T_1-weighted basis. However, it still would not be obvious to combine Platzek et al.'s paramagnetic perflouroalkyl-containing agents with the perflouroalkyl-containing agents of Mattrey because the paramagnetic effect of the Platzek compounds would have an adverse effect on the ^{19}F-based image. Thus, this would be the opposite of motivation to combine. This is because the presence of a paramagnetic ion in a fluorine-containing chelate, such as that of Platzek et al., results in a strong dipolar interaction of the nuclei. This produces a large broadening of the F-based signal in ^{19}F magnetic resonance imaging. The broadening of the single results in an enormous decrease of signal intensity. That is, the ^{19}F images become black. The same thing happens when a paramagnetic perflouroalkyl-containing compound is added to a perflouro diamagnetic compound for the purposes of ^{19}F imaging. Thus, there is

no motivation to employ the recited paramagnetic compounds in conjunction with the recited diamagnetic compounds even in ^{19}F MRI.

As can be seen, the prior art rejection is unsound and must be withdrawn.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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Perfluorooctylbromide: A New Contrast Agent for CT, Sonography, and MR Imaging

Robert F. Mattrey[1]

Perfluorochemicals are a class of compounds composed entirely of carbon and fluorine atoms. They were made famous when Clark and Gollan [1] demonstrated their oxygen-carrying potential by submerging normal mice in the liquid for an extended period of time. These mice suffered no ill effects while they were submerged or afterward [1]. Perfluorochemicals, like oil, are immiscible with water and cannot be given intravenously unless emulsified [2]. Fluosol-DA (Alpha Therapeutics Corp., Los Angeles, CA) and PFOB-100% (Fluoromed Pharm, La Mesa, CA) are two emulsions that have been given intravenously to human subjects [3, 4].

Perfluorooctylbromide (PFOB), a fluorochemical in which one bromine atom is substituted for fluorine, is radiopaque on radiography and CT [5–10]. PFOB has been used in human subjects in its neat form (pure unemulsified liquid) for radiography of the gastrointestinal tract and for bronchography (Long DM, unpublished data). IV perfluorochemical emulsions given to animals [11–13] and humans [14] are effective sonographic contrast agents. Because these compounds, in the neat form, have no hydrogen atoms, they are effective negative oral contrast agents for MR imaging [15, 16]. These agents can also be imaged with MR when coils are tuned to the Larmor frequency of the ^{19}F nucleus [17]. Clinical trials with IV PFOB as a CT and a sonographic contrast agent have begun in Europe. Preliminary reports are extremely encouraging [4].

Physical Properties, Pharmacokinetics, and Toxicity of PFOB

Perfluorochemicals, including PFOB, are inert and have high gas solubility, low surface tension, and very low toxicity when ingested or inhaled [18, 19]. Because of these unique properties they are used extensively in industry as cleansers, lubricants, and propellants [18]. These compounds actually behave like a liquefied gas. Some are extremely volatile, like freon, whereas others are extremely stable. They accumulate in human tissues when inhaled, ingested, or given intravenously. The length of time they remain in the body is related to their molecular weight and vapor pressure (volatility); the more volatile they are the shorter their half-life, which can range from minutes to years [20, 21]. Those with very short half-lives (hours) cannot be used intravenously because they produce pulmonary emphysema as they evaporate out of the pulmonary capillaries into the interstitium [21]. IV PFOB-100%, given to rats at a dose of 1.5 g/kg, has a half-life of 3 days, which is long enough to be safe and short enough to be practical [22]. Fluosol-DA 20%, the first perfluorochemical used in humans intravenously, consists of two perfluorochemicals, perfluorodecalin and perfluorotripropylamine (their half-lives are 6 and 63 days, respectively) [21].

PFOB, which is twice as dense as water, is emulsified in pure lecithin to produce 100% weight per volume emulsion

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(1 g PFOB in 1 ml emulsion) with particle sizes 0.1- to 0.2-μm in diameter [23]. These particles, unable to leak out of normal capillaries, are limited to the intravascular space. PFOB is removed from blood by two competitive mechanisms, phagocytosis by the reticuloendothelial system and evaporation through the lung. In rats, the PFOB half-life in blood was approximately 6 hr after the infusion of 2.5 g/kg [22]. In rats, 99.8% of the IV PFOB dose is eliminated in the expired air. The remainder is eliminated in feces during the first few days, probably from bile excretion, and none is eliminated in urine [22]. Early clinical data from the European trials suggest a shorter blood half-life in man.

IV PFOB is eliminated without breakdown of its chemical structure. No acute hemodynamic effects of the lecithin-based 100% PFOB emulsion occurred when 1 g (1 ml)/kg was given as an IV bolus to dogs (Mattrey RF, unpublished data). The 7-day LD_{50} of PFOB in rats is 45 g/kg with an LD_{50} to diagnostic dose ratio of 22:1 [22]. No subacute or chronic toxicity of PFOB is expected.

More than 95% of the oral PFOB dose is excreted by the gastrointestinal tract within 24 hr [5]. No LD_{50} could be measured in rats when dosages in excess of 64 ml/kg were ingested [5, 24]. PFOB has been taken orally by approximately 60 human subjects at dosages of 2–12 ml/kg. Extensive laboratory studies before and at various time intervals up to 3 days after PFOB ingestion showed no effect [15, 16]. Although some absorption occurs after ingestion, minuscule levels are detectable in tissues that are five orders of magnitude smaller than would be found if 1 g/kg were given intravenously. An IV dose of 1 g/kg has no detectable toxic effect [22].

Computed Tomography

Although urographic contrast agents are ideal for renal CT scanning, they are suboptimal for imaging the blood pool and various organs on CT. These agents are lost to the extravascular space because they quickly diffuse into and equilibrate with the interstitial fluid. Because PFOB remains intravascular, the dose can be titrated to provide the blood enhancement desired on CT, and the degree of enhancement will be the same throughout the arteries, veins, and cardiac chambers (Fig. 1) [9]. With the 6-hr blood half-life of PFOB, this enhancement persists long enough to allow ample time for CT imaging. Tissues enhance to a degree commensurate with their blood volume [25]. Blood-pool enhancement of tissues with PFOB on CT is comparable to labeled RBC blood-pool scanning in nuclear medicine. PFOB on CT should allow the differentiation of intrahepatic tumors from hemangiomas, because intrahepatic tumors have less blood than liver does and hemangiomas are essentially a blood pool. This hypothesis would of course require testing in the clinical setting.

EOE-13 (ethiodized oil emulsion), like PFOB, is taken up by the reticuloendothelial system of the liver and spleen [8, 26]. EOE-13 does not enhance blood vessels. It has a sensitivity of 90% for the detection of liver tumors, which is considered to be the best of all CT techniques [27]. The reason for the less than perfect sensitivity is because small lesions are confused with comparable-sized intrahepatic vessels and vice versa [28]. However, unlike EOE-13 enhancement, the simultaneous enhancement of the vascular space with PFOB renders lesions the only unopacified structures within the liver (Fig. 2), potentially providing greater than the 90% sensitivity in the detection of liver lesions achieved with EOE-13.

Within minutes to hours after PFOB is given, enhancement of abscess wall and tumors begins; enhancement peaks at 1–4 days. Accumulation of PFOB in these sites is thought to occur by either transcapillary leak through abnormal neoplastic or inflammatory vascular beds, accumulation of PFOB-filled macrophages, or both. That transcapillary leakage occurs is evidenced by tumor rim enhancement minutes after infusion [29] and the presence of PFOB particles in the perivascular space when lecithin is stained with a fat stain [17]. By 48 hr, all of PFOB in these sites is within macrophages that are then present in large numbers when compared with controls [8, 10]. It is not clear how these PFOB-filled macrophages accumulate in lesions. They may have taken up PFOB elsewhere, become activated as has been suggested [30], and accumulated in immunologically active sites; or they may have been residents of these sites or recruited to these sites to phagocytose the PFOB particles present in the interstitium.

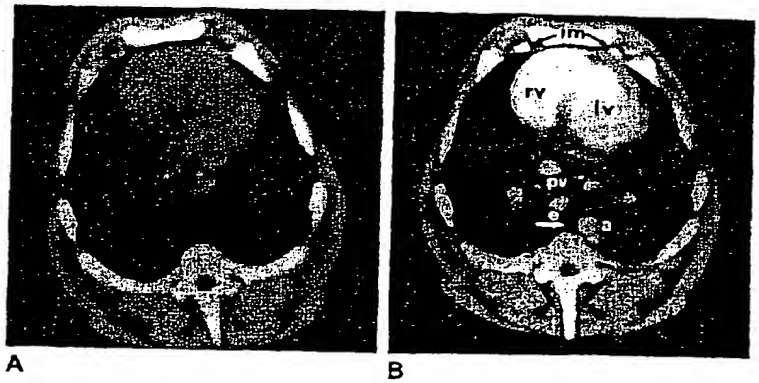

Fig. 1.—Transverse CT scans at level of heart in pig before and after IV administration of 5 g/kg perfluorooctylbromide (PFOB).

A, Before PFOB. All vascular and nonvascular structures are isodense.

B, 50 min after PFOB. All vascular structures are markedly enhanced to same degree, including intrapulmonary vessels (pv). There is marked enhancement of internal mammary vessels (im). Enhanced descending aorta (a) is recognized from esophagus (e). rv = right ventricle; lv = left ventricle.

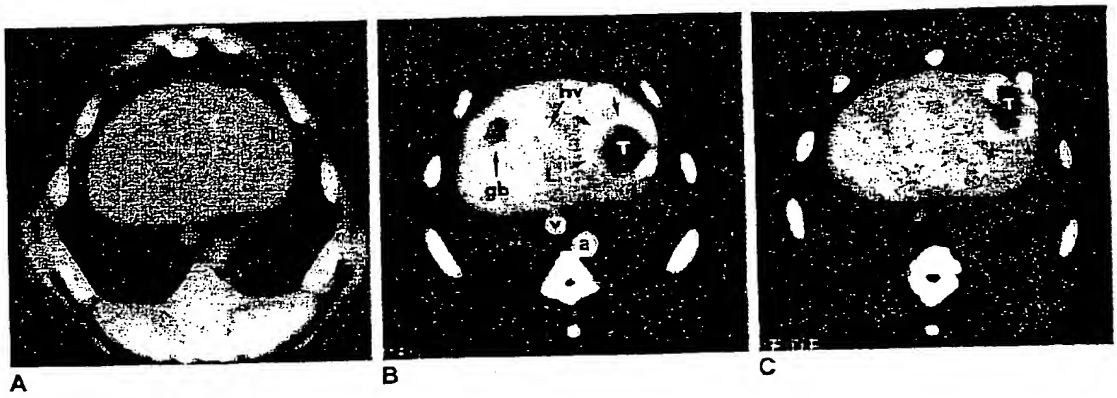

Fig. 2.—Transverse CT scans of rabbit at level of V×2 tumor implanted in liver.
A, Before perfluorooctylbromide (PFOB). Tumor (T) is isodense relative to liver and paraspinal muscles.
B, 5 min after 5 g/kg PFOB. Liver (L) and blood vessels, including intrahepatic veins (hv), enhance significantly relative to tumor and paraspinal muscles. There is a faint hypervascular tumor rim (*small arrows*).
C, 48 hr later. Tumor rim has become hyperintense relative to liver (*arrows*).
a = aorta; v = vena cava; gb = gallbladder.

Lesion enhancement has been documented by both CT and sonography after the administration of PFOB [8, 10–13, 29]. In fact, it appears that PFOB accumulates in any region where macrophages are found, including tumors [8, 11, 12, 14, 29], abscesses [10, 31], and injured [32] or infarcted [13] tissues. This leads to enhancement of the area on CT in proportion to the degree of inflammation [32]. An application of great clinical potential may be the use of PFOB as a CT contrast agent to improve the detection of abscesses. In rabbits in which hepatic and peritoneal abscesses were induced, PFOB produced dense enhancement of abscess wall on CT 2 days after infusion of the compound [10]. Although liquefied centers of hepatic abscesses could be seen without PFOB, PFOB made it possible to determine the extent of the inflammation (Fig. 3). Although the peritoneal abscesses were not visible on CT without PFOB, they were all identified after PFOB administration [10].

Sonography

Perfluorochemicals are effective contrast agents for sonography [11, 12]. The echogenicity of perfluorocarbons is due to their high density (1.9 g/ml) and low acoustic velocity (600 m/sec), imparting an acoustic impedance difference of 30% with tissues. Because impedance difference determines the brightness of the echo, and because the impedance of tissues (except for fat) differ by 1–5%, perfluorochemicals are highly reflective. Thus, the presence of PFOB particles in tissues increases the number and brightness of interfaces and therefore echogenicity.

PFOB enhances tissues during its vascular phase immediately after infusion [29]. The degree of enhancement is commensurate with the degree of perfusion. Hypovascular renal tumors that have the same or greater echogenicity than the kidney become less echogenic immediately after PFOB infusion [29]. This is also true of liver tumors (Fig. 4). Increased echogenicity in proportion to the degree of vascularity may allow sonography to be used to estimate the degree of tissue perfusion, visualize areas of infarction, and tumors.

Doppler signals and their color rendition enhance significantly as a result of PFOB [33], which lasts for hours because of the long blood half-life of PFOB. Doppler signals, including color, become detectable from submillimeter vessels as well as vessels not seen on the gray-scale image [33]. This capability should have a significant impact on deep Doppler applications, where small or deep vessels reflect weak signals.

Perfluorochemicals also enhance the liver and spleen because of their uptake by the reticuloendothelial cells for at least 2 days after their administration [11–14]. In humans, Fluosol-DA 20% produced significant liver and spleen enhancement 24 hr after a dose of 2.4 g/kg, allowing the visualization of unenhanced tumors [14].

As with CT, macrophages that accumulate in lesions become visible sonographically. In patients, the IV administration of Fluosol caused significant rim or diffuse echogenic enhancement of colonic, pancreatic, and gastric liver metastases at dosages of 1.6 and 2.4 g/kg, allowing the visualization of previously missed lesions [14].

MR Imaging

PFOB as an Oral MR Contrast Agent

Neat perfluorocarbons have potential as MR oral contrast agents because (1) lacking hydrogen, they cause no MR signal, and therefore, like air, they darken bowel lumen on both T1- and T2-weighted images; (2) being immiscible with water, they produce a signal void that is independent of bowel content; (3) they have a more rapid transit through bowel than

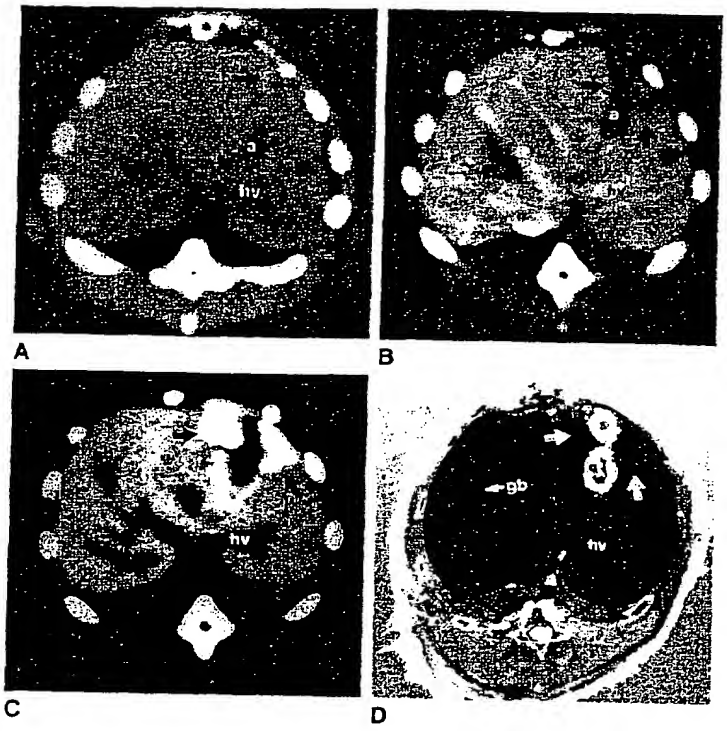

Fig. 3.—Transverse CT scans of rabbit at level of abscess in liver.

A, Before perfluorooctylbromide (PFOB). Faint calcification is seen at abscess (a) margin (*arrow*).

B, 5 min after 5 g/kg PFOB. Liver and blood vessels, including intrahepatic veins (hv), enhance significantly relative to abscess, phlegmon about abscess (*arrows*), and paraspinal muscles. Phlegmon does not enhance significantly.

C, 48 *hr* later. Dense enhancement of phlegmon (*arrows*) extends beyond abscess wall. Intrahepatic vessels are less dense than liver.

D, Anatomic section at approximate level of *C* shows phlegmon (*arrows*) extending beyond confines of abscess.

gb = gallbladder.

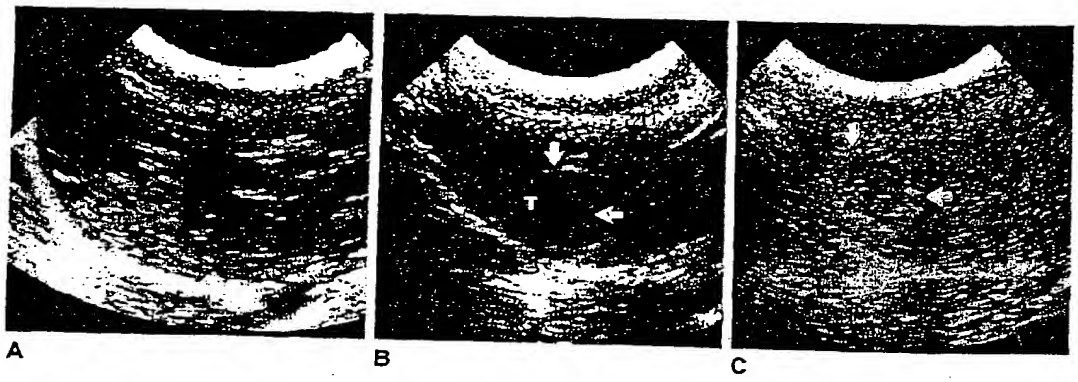

Fig. 4.—Longitudinal sonograms of liver at level of V×2 tumor of rabbit in Fig. 2.

A, Before perfluorooctylbromide (PFOB). Tumor (T) is hyperechoic relative to surrounding liver.

B, 30 min after 5 g/kg PFOB. Tumor is hypoechoic relative to liver. There is faint rim enhancement (*arrows*).

C, 48 *hr* later. Tumor rim is echogenic (*arrows*).

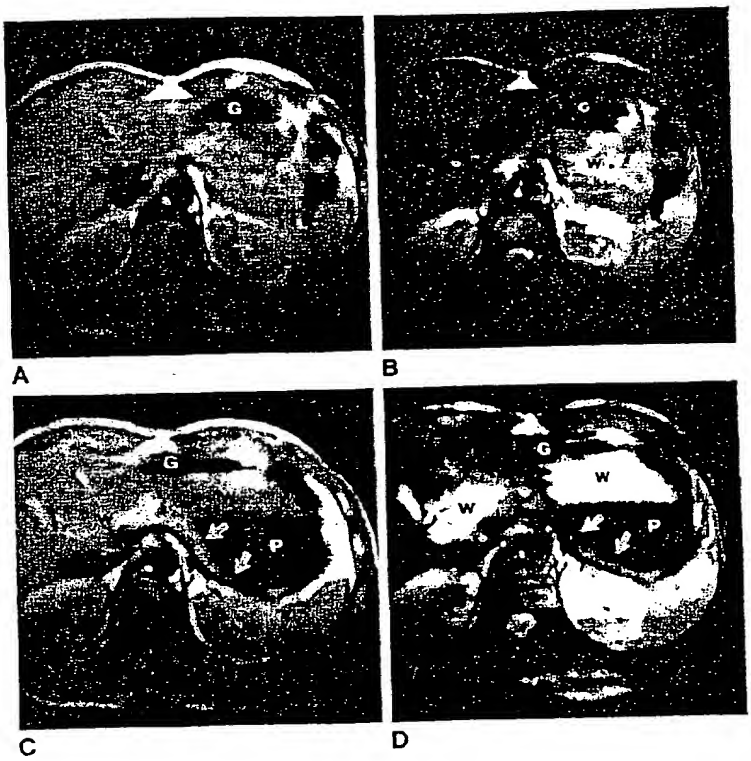

Fig. 5.—Transverse MR images at level of pancreas of volunteer before and after ingestion of 500 ml neat perfluorooctylbromide (PFOB).

A and *B*, Hydrogen-density (2000/20) (*A*) and T2-weighted (2000/70) (*B*) images before PFOB ingestion. Pancreas is not visible because of water (W) in gastric fundus.

C and *D*, Hydrogen-density (*C*) and T2-weighted (*D*) images obtained with same technique 5 min after PFOB ingestion. Clear visualization of pancreas (*arrows*) contrasts with PFOB-filled gastric fundus. Air-fluid-fluid level with water (W) floating between gas (G) and PFOB (P).

barium or Hypaque because of their low surface tension [5]; and (4) they are tasteless, odorless, and have no side effects [5, 24]. The use of PFOB was shown to be feasible in rats and humans [15]. PFOB significantly darkened bowel lumen on T1-weighted, hydrogen-density, and T2-weighted images (Fig. 5) [16].

MR Imaging of the ^{19}F Nucleus

Fluorine is the next best nucleus for MR applications after hydrogen, because it has 100% natural isotopic abundance and has an 83% sensitivity relative to hydrogen. ^{19}F in PFOB can be imaged to show the vascular pool, liver, spleen, and macrophage collections [17, 34].

^{19}F MR imaging or spectroscopy can be used to estimate tissue oxygen tension percutaneously. Neat PFOB can carry more than twice as much oxygen as whole blood can [2]. Dissolved molecular oxygen is paramagnetic, affecting T1 shortening of ^{19}F [35]. Tissue oxygen tension can be estimated by appropriate MR techniques, because oxygen in perfluorocarbons is carried passively and is in equilibrium with tissue oxygen tension [2], and the ^{19}F relaxation rate is linearly related to oxygen tension dissolved in the perfluorocarbon [35]. Fishman et al. [36] showed signal-intensity changes in various tissues in rats when respired oxygen tension was changed from 20% to 100%. Therefore, these agents can be used to detect ischemic tissues and to monitor the efficacy of therapy. Although this technique is feasible and of great interest, its accuracy and potential utility in vivo have not yet been documented.

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